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Patients with drug-refractory atrioventricular nodal reentrant tachycardia: Clinical features, electrophysiological characteristics, and predictors of medication failure

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ABSTRACT

Background and purpose: Drug responses vary markedly from patient to patient in atrioventricular nodal reentrant tachycardia (AVNRT), the most common form of paroxysmal regular supraventricular tachycardia in adults. However, clinical and electrophysiological (EP) characteristics of patients with AVNRT whose tachycardia attacks could not be adequately controlled by antiarrhythmic agents have not been studied in a large patient cohort. We aimed to define the clinical and EP features of patients with drug-refractory AVNRT.

Methods and results: A total of 266 consecutive patients with AVNRT undergoing catheter ablation after a period of medical treatment were analyzed: 144 patients with drug-refractory AVNRT (Group 1) and 122 patients with drug-responsive AVNRT (Group 2). Age was significantly higher ($p = 0.027$) and the presence of hypertension ($p = 0.030$), diabetes mellitus ($p = 0.047$), and valvular heart diseases ($p = 0.008$) was more frequent in Group 1 compared to Group 2. Among the EP features, atrial-His jump (81% vs 69%, $p = 0.028$) and atrial vulnerability (26% vs 14%, $p = 0.018$) were significantly higher, echo zone was significantly more long-lasting (44 ± 24 ms vs 38 ± 22 ms, $p = 0.018$), and tachycardia cycle length (TCL) was significantly longer (348 ± 41 ms vs 329 ± 38 ms, $p = 0.000$) in Group 1 than in Group 2. Multivariate analysis showed that hypertension ($p = 0.036$), valvular heart disease ($p = 0.014$), atrial vulnerability ($p = 0.037$), TCL ($p = 0.003$), and wide echo zone ($p = 0.028$) were independent predictors for drug-refractory AVNRT.

Conclusion: In the presence of hypertension, valvular heart disease, atrial vulnerability, long-lasting echo zone, and relatively slow AVNRT, medical treatment is less likely to prevent the tachycardia episodes.

Introduction

Atrioventricular nodal reentrant tachycardia (AVNRT) is the most common form of paroxysmal regular supraventricular tachycardia (SVT) in adults, accounting for 60% of the cases [1]. Radiofrequency (RF) catheter ablation has become the first-line treatment approach with high acute success and low complication rates [2–4]. On the other hand, antiarrhythmic therapy still plays a role in the majority of patients in the acute and long-term management of SVT [5]. However, drug responses vary markedly from patient to patient in AVNRT, satisfactory control being achieved in only 60% of the cases [6–8]. Even the so-called tailored therapy regimens as directed by electrophysiological (EP) studies before initiation of antiarrhythmic treatment can barely reach success rates of 70–80% [9–12]. Thus, drug-refractory AVNRT is a considerable health problem hampering the individual's quality of life [13]. Data are not yet available about the clinical characteristics and EP features of patients with drug-refractory AVNRT. The aim of this study was to compare clinical and EP characteristics as well as catheter ablation results in patients with drug-responsive and drug-refractory AVNRT.

Methods

Patients

The subjects of this study consist of 266 consecutive patients treated with RF catheter ablation for symptomatic AVNRT. All

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patients had a history of paroxysmal palpitations ranging from 6 months to 26 years. The frequency of tachycardia attacks documented on electrocardiographic (ECG) or Holter recordings varied from at least once in a month to three to four attacks in a year. Patients who experienced at least one documented episode of AVNRT in the previous 3 months before ablation despite maximum tolerable doses of antiarrhythmic agents were taken as the study group ($n = 144$; Group 1). Patients who did not have any palpitations on medications in the previous 6 months but opted to discontinue medication and undergo catheter ablation served as the control group ($n = 122$; Group 2). Patients with poor drug compliance or different EP diagnoses other than AVNRT were excluded from the study. The study was approved by the institutional ethical committee and informed written consent was obtained from each patient for the ablation procedure.

All the patients underwent 12-lead surface ECG, X-ray examination, echocardiography, and blood chemistry measurements including thyroid testing and, when clinically indicated, stress test and 24-h Holter ECG recording.

EP study and RF catheter ablation

EP study and catheter ablation were performed in a single session in all patients in the fasting, unsedated state and after discontinuation of all antiarrhythmic drugs for at least five half-lives. The standard protocol consisted of decremental high right atrial (A_1A_1) pacing, usually starting from 600 ms and decreasing in steps of 10 ms until the atrioventricular (AV) node Wenckebach cycle length was reached, and single atrial extrastimulus (A_1A_2) testing at three different drive train cycle lengths (600, 500, and 430 ms) to induce tachycardia. During pacing with the first drive train, the A_1–A_2 interval was shortened by 10 ms until the AV node effective refractory period (ERP) had been reached. A jump of the atrial-His bundle (AH) interval was defined as the difference between any consecutive AH intervals equal to or more than 50 ms during programmed or incremental atrial pacing. Programmed electrical stimulation was performed from the right ventricle to investigate the ventriculoatrial (VA) conduction at baseline. All basic EP data were collected with the patients unsedated and before infusion of any pharmacological stimulants except for tachycardia parameters in those patients whose tachycardia could be induced only under pharmacologic stimulation. AVNRT was diagnosed according to the standard criteria [1,14].

Slow pathway ablation was done with the integrated (electrogram-guided anatomic) approach, using 7 Fr quadripolar tip-deflectable catheters with 4-mm tip electrodes (Marinr MC, Medtronic Co., Minneapolis, MN, USA). Fifty watts of energy with a temperature limit of 65 °C was applied at successful sites for 60–90 s. RF delivery was terminated if junctional rhythm did not appear in the first 15 s and the catheter was moved to the mid- and anterior septum to repeat the procedure until the endpoints were reached. The endpoints of ablation were the demonstration of either a slow pathway block or a slow pathway modification with no more than one single echo beat along with noninducibility of AVNRT.

Follow-up after RF catheter ablation

All the patients were discharged 2 days postoperatively. After hospital discharge, all patients were scheduled for a visit 4–6 weeks later and every 3 months thereafter in the first year. If palpitations recurred, the patients were asked to obtain an ECG as soon as possible and contact our center.

Statistical analysis

Continuous variables were expressed as mean ± standard deviation. Groups were compared by means of chi-square analysis or Fischer's exact test when needed for discrete variables and with unpaired Student's t test for continuous variables.

Logistic regression analysis was used to examine and determine the predictors for drug-refractory AVNRT. The following variables were put into the model: age, gender, duration of symptoms, presence of hypertension, diabetes mellitus, valvular heart disease, coronary artery disease, left ventricular hypertrophy, left ventricular ejection fraction, and EP parameters; AV node Wenckebach cycle length, AV node anterograde ERP, presence of AH jumps, multiple AH jumps, echo zone duration, atrial vulnerability, the frequency of using pharmacologic stimulation to induce AVNRT, type of AVNRT, and tachycardia cycle length (TCL). Variables with $p < 0.20$ in univariate analyses were included into the multivariate analyses. In multivariate analysis, backward LR elimination was used to compare and build the appropriate model. Likelihood ratio values were considered for the reduction of the model.

Statistical comparisons were performed using the statistical software package SPSS 15.0 (SPSS Inc., Chicago, IL, USA). Calculated p-values of less than 0.05 were considered significant.

Results

The study group (Group 1) included 144 patients (79 women and 65 men; mean age 43 ± 15 years, range 17–84 years) and the control group (Group 2) consisted of 122 patients (64 women and 58 men; mean age 39 ± 14 years, range 20–78 years).

Clinical characteristics

Clinical characteristics of groups are shown in detail in Table 1. Age was significantly higher ($p = 0.027$) and hypertension ($p = 0.030$), diabetes mellitus ($p = 0.047$), and valvular heart diseases ($p = 0.008$) were more frequent in Group 1 as compared to Group 2. There was no difference between the study and control groups regarding the antiarrhythmic therapy regimen (Table 1).

Electrophysiological characteristics

The presence of discontinuous AV conduction was more frequent ($p = 0.028$) and the echo zone was seen to last slightly but significantly longer (44 ± 24 ms vs 38 ± 22 ms, $p = 0.018$) in Group 1 than in Group 2. The TCL was significantly longer in Group 1 ($p < 0.001$). The lower rate of AVNRT was due to the longer AH intervals ($p = 0.019$) in this group. The His-ventricle and VA intervals during tachycardia did not differ between the groups ($p > 0.05$ for both). The need for pharmacological stimulation to induce tachycardia did not differ between the groups ($p > 0.05$). EP characteristics of patients are shown in detail in Table 2.

Sustained atrial fibrillation (AF) lasting for more than 30 s was induced (atrial vulnerability) in 54 of 266 patients during EP study. Thirty-seven of these cases were in Group 1 (26%) and 17 were in Group 2 (14%) ($p = 0.018$). AF was converted spontaneously into sinus rhythm in the first 15 min in 47 patients (87%) and was electrically converted in 7 patients (13%). AF was induced through the degeneration of AVNRT in eight patients (15%); of these, three were in Group 1 and 5 in Group 2, the difference between the groups not being statistically significant ($p > 0.050$). AF was induced during programmed atrial stimulation or burst pacing in the rest of the 46 patients (85%). AF occurring during catheter manipulation was not taken into consideration.

A comparison of the EP variables of the groups with regard to the antiarrhythmic drugs failed to reveal any additional statistically significant difference between the groups. Among patients taking

Table 1
Baseline clinical characteristics of groups.

	Group 1 ($n=144$)	Group 2 ($n=122$)	p
Age (years), mean ± SD (range)	43 ± 15 (17–84)	39 ± 14 (20–78)	0.027
Male/female	65/79	58/64	ns
Systemic hypertension, *n* (%)	41 (29)	21 (17)	0.030
Diabetes mellitus, *n* (%)	31 (22)	15 (12)	0.047
Structural heart disease			
Valvular heart disease, *n* (%)	30 (21)	11 (9)	0.008
Coronary artery disease, *n* (%)	21 (15)	17 (14)	ns
Left ventricular hypertrophy, *n* (%)	23 (16)	10 (8)	0.055
LVEF < 50%, *n* (%)	12 (8)	6 (5)	ns
Duration of symptoms (years)	9.0 ± 6.3	7.7 ± 6.0	ns
Frequency of tachycardia (attacks/6-month)			
before antiarrhythmics	3.9 ± 1.4	3.7 ± 1.3	ns
after antiarrhythmics	2.8 ± 0.9	0	0.000
Exercise provokable tachycardia, *n* (%)	59 (41)	60 (49)	ns
Medication			
Beta-blocker, *n* (%)	57 (40)	49 (40)	ns
Calcium-channel blockers, *n* (%)	52 (36)	50 (41)	ns
Other antiarrhythmics,[a] *n* (%)	16 (11)	7 (6)	ns
Combined antiarrhythmics, *n* (%)	19 (13)	16 (13)	ns

LVEF, left ventricular ejection fraction; ns, not significant.
[a] Class-I or Class-III antiarrhythmic agents.

beta-blockers or calcium-channel blockers, discontinuous AV conduction (83% in Group 1 vs 67% in Group 2, $p=0.008$), echo zone width (47 ± 21 ms in Group 1 vs 37 ± 22 ms in Group 2, $p=0.002$), TCL (349 ± 44 ms in Group 1 vs 330 ± 41 ms in Group 2, $p=0.002$), and atrial vulnerability (28% in Group 1 vs 11% in Group 2, $p=0.002$) were seen to differ significantly between the groups. However, when the patient subgroups taking antiarrhythmic agents other than beta-blockers or calcium-channel blockers were analyzed, it was observed that only TCL (345 ± 33 ms vs 323 ± 24 ms, $p=0.007$) differed significantly while discontinuous AV conduction (74% vs 78%, $p>0.05$), atrial vulnerability (17% vs 26%, $p>0.05$), and the echo zone (37 ± 29 ms vs 39 ± 20 ms, $p>0.05$) did not show any significant difference between Group 1 and Group 2, respectively.

RF catheter ablation and follow-up after ablation

The results of RF ablation are shown in Table 3. AVNRT was eliminated with right endocardial approach in all cases except one, which was successfully ablated from the mitral septum. No difference was noted between the groups with respect to the successful ablation site in Koch's triangle.

Transient second-degree Mobitz type I AV block lasting less than 30 s was seen in two patients (1%) in Group 1 and one patient (1%) in Group 2 ($p>0.050$). Permanent PR prolongation was observed in three patients (2%) in Group 1 and one patient (1%) in Group 2 ($p>0.050$). One patient in Group 1, in whom AV conduction was intact during and after the ablation procedure, developed symptomatic intermittent third-degree AV block 3 months after the procedure and received a permanent pacemaker.

There were no differences between the groups with respect to the number of RF pulses (5.0 ± 2.8 in Group 1 and 4.9 ± 2.5 in Group 2; $p>0.050$), procedure duration (42 ± 18 min in Group 1 and 40 ± 16 min in Group 2; $p>0.050$), and total fluoroscopy duration (13 ± 6 min in Group 1 and 12 ± 6 min in Group 2; $p>0.050$).

During follow-up, recurrence of AVNRT was observed in three patients and all of them were treated successfully with a second session. The recurrence rate of AVNRT did not differ between the groups ($p>0.05$, Table 3).

Predictors for drug-refractory AVNRT

The factors associated with drug-refractory AVNRT are shown in Table 4. In univariate analysis, significant predictors for drug-refractory AVNRT were age ($p=0.028$), hypertension ($p=0.032$), diabetes mellitus ($p=0.049$), valvular heart disease ($p=0.010$), atrial vulnerability ($p=0.019$), discontinuous AV conduction

Table 2
Electrophysiological characteristics of groups.

	Group 1 ($n=144$)	Group 2 ($n=122$)	p
AV node WCL (ms)	326 ± 30	323 ± 33	ns
AV node antegrade ERP (ms)	230 ± 20	233 ± 23	ns
Maximum AH interval (ms)	319 ± 35	318 ± 37	ns
AH jump, *n* (%)	116 (81)	84 (69)	0.028
Multiple AH jumps, *n* (%)	22 (15)	15 (12)	ns
1:1 VAC	129 (90)	103 (84)	ns
Echo zone (ms) mean ± SD	44 ± 24	38 ± 22	0.018
Atrial vulnerability, *n* (%)	37 (26)	17 (14)	0.018
Type of AVNRT			
Typical, *n* (%)	135 (94)	113 (93)	ns
Atypical, *n* (%)	9 (6)	9 (7)	ns
Tachycardia parameters			
TCL (ms)	348 ± 41	329 ± 38	0.000
AH interval	228 ± 50	214 ± 50	0.019
hRA-VA interval (ms)	74 ± 27	71 ± 31	ns
Atropine, *n* (%)	32 (22)	26 (21)	ns

AV, atrioventricular; WCL, Wenckebach cycle length; ERP, effective refractory period; AH, atrial-His bundle; 1:1 VAC, 1:1 ventriculoatrial conduction; AVNRT, atrioventricular nodal reentrant tachycardia; TCL, tachycardia cycle length; hRA-VA, ventriculoatrial interval at the high right atrium; ns, not significant.

Table 3
Results of radiofrequency catheter ablation.

	Group 1 ($n=144$)	Group 2 ($n=122$)	p
Success rate, n (%)	144 (100)	122 (100)	ns
Successful ablation site			
Midseptal, n (%)	81 (56)	65 (53)	ns
Posteroseptal, n (%)	62 (43)	57 (47)	ns
Left midseptal, n (%)	1 (1)	0	ns
PR prolongation, n (%)	3 (2)	1 (1)	ns
Transient AVB, n (%)	2 (1)	1 (1)	ns
Permanent complete AVB, n (%)	1 (1)	0	ns
Residual dual pathway, n (%)	28 (19)	26 (21)	ns
Residual single echo beat, n (%)	18 (13)	14 (12)	ns
Recurrence of AVNRT, n (%)	1 (1)	2 (2)	ns
Follow-up duration (months)	22 ± 10	23 ± 11	ns

AVNRT, atrioventricular nodal reentrant tachycardia; AVB, high-grade atrioventricular block; ns, not significant.

Table 4
Univariate and multivariate predictors for drug-refractory AVNRT.

	RR	95% CI	p
Univariate predictors			
Age	1.019	1.002–1.036	0.028
Hypertension	1.914	1.058–3.465	0.032
Diabetes mellitus	1.957	1.001–3.827	0.049
Valvular heart disease	2.656	1.269–5.558	0.010
Atrial vulnerability	2.136	1.133–4.027	0.019
Discontinuous AV conduction	1.874	1.067–3.291	0.029
TCL	1.012	1.006–1.019	0.000
Echo zone	1.013	1.002–1.024	0.019
Multivariate predictors			
Hypertension	1.975	1.045–3.733	0.036
Valvular heart disease	2.628	1.215–5.688	0.014
Atrial vulnerability	2.039	1.044–3.982	0.037
Echo zone	1.013	1.001–1.025	0.028
TCL	1.010	1.003–1.017	0.003

TCL, tachycardia cycle length; AV, atrioventricular; RR, relative risk; CI, confidence interval.

($p=0.029$), TCL ($p=0.000$), and wide echo zone ($p=0.019$). However, using the multivariate analysis, two clinical and three EP features emerged as independent predictors for drug-refractory AVNRT. Clinical features were hypertension ($p=0.036$) and valvular heart disease ($p=0.014$). Independent EP predictors were atrial vulnerability ($p=0.037$), TCL ($p=0.003$), and echo zone ($p=0.028$) (Table 4).

Discussion

This study analyzes the clinical and EP characteristics of patients with AVNRT whose tachycardia episodes could not be controlled with the most common antiarrhythmic agents. The results of this study demonstrate that patients with drug-refractory AVNRT tend to be older, and more commonly suffer from valvular heart disease, diabetes mellitus, and hypertension when compared to those patients whose tachycardia is well controlled medically. Among the EP data, AH jumps in the AV conduction curve and atrial vulnerability were more frequent, echo zones were more long-lasting, and TCL were slightly but significantly longer in patients with drug-refractory AVNRT. Hypertension, valvular heart disease, atrial vulnerability, lower rates of AVNRT, and wide echo zones were identified as independent predictors for drug-refractory AVNRT.

In our study, drug therapy is seen to be less efficacious in patients with relatively slower AVNRT. In a previous study, Ballo et al. [15] have reported that verapamil is less effective in patients with paroxysmal SVT with higher rates and suggested that the rate of tachycardia may have a definitive role in the acute treatment of paroxysmal SVT. Although these results are not compatible with ours, there are two important differences in the study designs. First, their study involved patients with paroxysmal SVT; the number of patients diagnosed with AVNRT is not known. AVNRT cases have been evaluated along with tachycardia types having entirely different EP properties such as atrial tachycardia or atrioventricular reentrant tachycardia. It is well known that the rate of AV reentrant tachycardia is usually higher than the rate of AVNRT and different subtypes of paroxysmal SVT may show unequal responsiveness to antiarrhythmic agents [16]. Second, Ballo et al. studied the activity of verapamil in the conversion of ongoing SVT to sinus rhythm. Interruption of an ongoing reentry and prevention of initiation of a reentry involve different electropharmacological responses. The former involves interruption of a reentry cycle through alteration of ERP, while the latter targets elimination of triggers and/or prevention of activation of the reentry cycle by these triggers. As is known, the most common triggers for an episode of AVNRT are atrial or, sometimes, ventricular ectopic beats. Inability to suppress these ectopic beats effectively with current antiarrhythmic agents may be the fact behind high failure rates of medical therapy.

Consistent with our findings, Wu et al. studied the effects of propranolol on inducibility of AVNRT during EP study and found that propranolol could not prevent inducibility of AVNRT in cases with lower tachycardia rates [17]. Additionally, it has been suggested that a predominant parasympathetic modulation of the right atrial input to the AV node with a consequent conduction delay might have pro-arrhythmic effects in patients with AVNRT [18]. An increase in refractoriness in one pathway could be offset by an increase in the conduction time in the opposing pathway of the reentrant circuit.

Critical AH interval is of fundamental importance in the induction of AVNRT [19]. Another important factor in the inducibility of AVNRT is the echo zone, which is indirectly related to the critical AH interval. The echo zone is defined as the zone in which

atrial extrastimuli induce atrial echo beats with or without AVNRT [17,20]. The outer and inner limits of this zone are the longest and shortest A_1–A_2 stimuli followed by an atrial echo beat, respectively. Reentry is likely to be induced with extrastimuli slightly shorter than the outer limit of the echo zone and noninducible below the inner limit of the echo zone. Antiarrhythmic drugs have different EP effects [6,11,21]. It has been reported that Class Ic antiarrhythmic agents are more effective in the presence of wide echo zones and Class III agents in short-lasting ones [9,22,23]. However, among our patients using Class I or Class III agents, the width of the echo zone did not differ significantly between the drug-responsive and drug-refractory AVNRT groups, although it was slightly wider in the drug-refractory group. This could possibly result from the relatively small number of cases, as most patients undergo ablation at this stage. Besides, these drugs are known to decrease excitability, suppress spontaneous automaticity and triggered activity, and increase refractoriness in the atrial or ventricular myocardium as well as in the AV node, specifically on the retrograde fast pathway, all of which are important in both the initiation and continuation of the AVNRT [6]. Thus, when compared to drugs affecting predominantly the antegrade slow pathway, width of the echo zone may not be as important in controlling the tachycardia episodes with Class I or Class III drugs. On the other hand, there are no clear data about the efficacy of Class II or Class IV drugs in the prevention of AVNRT episodes with respect to the width of the echo zone. In our study, the echo zones were wider in drug-refractory AVNRT patients taking beta-blockers or calcium-channel blockers. The fact that the broader the echo zone, the more persistent the critical AH delay, which renders the AVNRT easier to trigger in daily life, could partly explain why drugs affecting predominantly the antegrade slow pathway, namely Class II or Class IV, are less effective in the prevention of AVNRT episodes in patients with wider echo zones.

Premature depolarizations are known to be important for the initiation of AVNRT, while sympathetic predominance helps sustain the tachycardia, as shown by Nigro et al. [24]. Higher incidence of structural heart disease and hypertension in Group 1 may contribute to the development of drug-refractory AVNRT attacks via both increased premature beats and sympathetic predominance in these patients. It has been suggested that reduced reflex vagal activity may contribute to the development of sustained AVNRT in patients with dual AV nodal physiology [25].

The incidence of paroxysmal AF is higher in patients with AVNRT than in the healthy population and is around 15–20% [26]. The presence of atrial vulnerability seems to be an important predictor in patients with coexisting AVNRT and AF. We have previously reported that in patients with AF and AVNRT attacks, the AF recurrence rates were significantly higher after successful ablation of AVNRT in those with atrial vulnerability [27]. The atrial refractory period, the dispersion of refractoriness, and intra- and inter-atrial conduction delays are considered determinants of atrial vulnerability [28]. In our study, atrial vulnerability was more frequent in patients with drug-refractory AVNRT. It is not possible to explain the reasons for this finding, as the study design did not involve searching for the causes of atrial vulnerability. It can be speculated that the electromechanical remodeling leading to atrial vulnerability might also enhance triggering and sustaining of AVNRT and hamper its response to drugs. Whether the autonomic or mechanical effects have a determining role in this process needs to be clarified by future studies.

Otomo and coworkers have shown that concealed atriohisian tracts exist in approximately one-third of patients with typical AVNRT, most of which are resistant to adenosine and possibly nondecremental, and they suggest that the lower turnaround of the reentrant circuit might be located within the His bundle in these patients [29]. Moreover, Akhtar et al. reported that such a retrograde fast pathway did not exhibit VA prolongation after administration of verapamil [30]. The mechanism responsible for such "Kent bundle-like" behavior of the retrograde fast pathway was considered to be retrograde bypass of the AV node [31,32]. Given the fact that beta-blockers or dihydropyridine group of calcium-channel blockers exerts their effects through reentry circuits with decremental behavior, the presence of concealed atriohisian tracts capable of nondecremental conduction or retrograde fast pathways with "Kent bundle-like" behavior could be responsible for drug-refractory AVNRT in some cases. The possible role of the unusual concepts of concealed atriohisian pathways, lower turnaround of the reentrant circuit inside the His bundle, or Kent bundle-like behavior of the retrograde fast pathway in the mechanism of drug-refractory AVNRT remains to be elucidated in future studies.

Study limitations

There is no standard objective definition for drug-refractory AVNRT in the literature. Some physicians might consider medical treatment successful in case of a single AVNRT attack in 6 months. We preferred not to define drug-refractory AVNRT with two or more attacks in 6 months so as not to leave a gray zone. Besides, in our study, the average number of attacks in the last 6 months was 2.8 ± 0.9. Thus, an attack frequency in this range can be considered appropriate to define failure of medical treatment.

In our study, approximately 80% of the patients in each group were taking beta-blockers or calcium-channel blockers, which are mentioned in current guidelines among Class I indications in the prevention of AVNRT recurrences. Patients taking beta-blockers or calcium-channel blockers could have been asymptomatic if they had used more potent Class I or Class III antiarrhythmic drugs or combined therapy, and vice versa. However, the purpose of our study was not to determine the stepwise efficacy of antiarrhythmic drugs, either single or combined, on AVNRT episodes.

Conclusion

The present study shows that hypertension, valvular heart disease, atrial vulnerability, wide echo zone, and relatively slow AVNRT are independent predictors for AVNRT that is likely unresponsive to more commonly prescribed antiarrhythmic drugs. These findings may help clinicians in the selection of the treatment modality.

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Conflicts of interest

None declared.

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References

[1] Elvas L, Gursoy S, Brugada J, Andries E, Brugada P. Atrioventricular nodal reentrant tachycardia: a review. Can J Cardiol 1994;10:342–8.
[2] Amasyali B, Kose S, Celik T. Atrioventricular nodal re-entrant tachycardia with QRS voltage and cycle length alternation and aberrant conduction due to two distinct antegrade slow pathways. Europace 2006;8:134–7.
[3] Efremidis M, Sideris A, Letsas KP, Alexanian IP, Pappas LK, Mihas CC, Manolatos D, Xydonas S, Gavrielatos G, Filippatos GS, Kardaras F. Potential-guided versus anatomic-guided approach for slow pathway ablation of the common type

atrioventricular nodal reentry tachycardia: a randomized study. Acta Cardiol 2009;64:477–83.
[4] Fenelon G, Elvas L, D'avila A, Tsakonas K, Malacky T, Manios E, Geelen P, Declerck L, Ramchurn H, De Vusser P. Radiofrequency ablation of atrioventricular node reentrant tachycardia: experience in 302 patients. Acta Cardiol 1995;50:397–410.
[5] Vassilikos VP, Mantziari L, Goudis CA, Paraskevaidis S, Dakos G, Stavropoulos G, Giannoglou G, Efthimiadis G, Mochlas S, Parcharidis G, Louridas G, Styliadis IH. Practice patterns of cardiologists, general practitioners, and internists for managing supraventricular tachycardias in Greece. Eur J Emerg Med 2011;18:153–6.
[6] Blomström-Lundqvist C, Scheinman MM, Aliot EM, Alpert JS, Calkins H, Camm AJ, Campbell WB, Haines DE, Kuck KH, Lerman BB, Miller DD, Shaeffer CW, Stevenson WG, Tomaselli GF, Antman EM, et al. ACC/AHA/ESC guidelines for the management of patients with supraventricular arrhythmias: executive summary. A report of the American College of Cardiology/American Heart Association task force on practice guidelines and the European Society of Cardiology committee for practice guidelines (writing committee to develop guidelines for the management of patients with supraventricular arrhythmias) developed in collaboration with NASPE-Heart Rhythm Society. J Am Coll Cardiol 2003;42:1493–531.
[7] Bauernfeind RA, Wyndham CR, Dhingra RC, Swiryn SP, Palileo E, Strasberg B, Rosen KM. Serial electrophysiologic testing of multiple drugs in patients with atrioventricular nodal reentrant paroxysmal tachycardia. Circulation 1980;62:1341–9.
[8] Rizos I, Seidl KH, Aidonidis I, Stamou S, Senges J, Toutouzas P. Intraindividual comparison of diltiazem and verapamil on induction of paroxysmal supraventricular tachycardia. Cardiology 1994;85:388–96.
[9] Manz M, Steinbeck G, Luderitz B. Usefulness of programmed stimulation in predicting efficacy of propafenone in long-term antiarrhythmic therapy for paroxysmal supraventricular tachycardia. Am J Cardiol 1985;56:593–7.
[10] Sarubbi B, Ducceschi V, Esposito R, Briglia N, Manzo G, Mayer MS, Santangelo L, Iacono A. The pharmacological treatment of supraventricular atrioventricular nodal reentry or accessory pathway reentry tachycardias: the usefulness of transesophageal electrophysiological study in the selection of therapy. Cardiologia 1996;41:543–9.
[11] Lüderitz B, Manz M. Pharmacologic treatment of supraventricular tachycardia: the German experience. Am J Cardiol 1992;70:66A–73A.
[12] Lévy S, Ricard P. Using the right drug: a treatment algorithm for regular supraventricular tachycardias. Eur Heart J 1997;18:C27–32.
[13] Larson MS, McDonald K, Young C, Sung R, Hlatky MA. Quality of life before and after radiofrequency catheter ablation in patients with drug refractory atrioventricular nodal reentrant tachycardia. Am J Cardiol 1999;84:471–3.
[14] Leitch J, Klein GJ, Yee R, Murdock C. Invasive electrophysiologic evaluation of patients with supraventricular tachycardia. Cardiol Clin 1990;8:465–77.
[15] Ballo P, Bernabò D, Faraguti SA. Heart rate is a predictor of success in the treatment of adults with symptomatic paroxysmal supraventricular tachycardia. Eur Heart J 2004;25:1310–7.
[16] Bottoni N, Tomasi C, Donateo P, Lolli G, Muià N, Croci F, Oddone D, Menozzi C, Brignole M. Clinical and electrophysiological characteristics in patients with atrioventricular reentrant and atrioventricular nodal reentrant tachycardia. Europace 2003;5:225–9.
[17] Wu D, Denes P, Dhingra R, Khan A, Rosen KM. The effects of propranolol on induction of A–V nodal reentrant paroxysmal tachycardia. Circulation 1974;50:665–77.
[18] Sinkovec M, Pernat A, Rajković Z, Jan M, Antolic B, Rakovec P. Electrophysiology of anterograde right-atrial and left-atrial inputs to the atrioventricular node in patients with atrioventricular nodal re-entrant tachycardia. Europace 2011;13:869–75.
[19] Denes P, Wu D, Amat-y-Leon F, Dhingra R, Wyndham CR, Rosen KM. The determinants of atrioventricular nodal re-entrance with premature atrial stimulation in patients with dual A–V nodal pathways. Circulation 1977;56:253–9.
[20] Pintarić H, Zeljković I, Babić Z, Vrsalović M, Pavlović N, Bosnjak H, Petrac D. Electrophysiological predictors of propafenone efficacy in prevention of atrioventricular nodal re-entrant and atrioventricular re-entrant tachycardia. Croat Med J 2012;53:605–11.
[21] Josephson ME. Supraventricular tachycardias. In: Josephson ME, editor. Clinical cardiac electrophysiology. Philadelphia: Lippincott Williams & Wilkins; 2008. p. 175–284.
[22] Nattel S, Gersh BJ, Opie LH. Antiarrhythmic drugs and strategies. In: Opie LH, Gersh BJ, editors. Drugs for the heart. Philadelphia: Saunders Elsevier Inc.; 2013. p. 272–331.
[23] Members of the Sicilian Gambit. The concept of the vulnerable parameter and its application to specific arrhythmias. In: Members of the Sicilian Gambit, editor. Antiarrhythmic therapy: a pathophysiologic approach. Armonk, NY: Futura Publishing Co. Inc.; 1994. p. 121–7.
[24] Nigro G, Russo V, de Chiara A, Rago A, Cioppa ND, Chianese R, Manfredi D, Calabrò R. Autonomic nervous system modulation before the onset of sustained atrioventricular nodal reentry tachycardia. Ann Noninvasive Electrocardiol 2010;15:49–55.
[25] Rigden LB, Mitrani RD, Rardon DP, Klein LS, Zipes DP, Miles WM. Reduced reflex vagal activity in patients with AV nodal reentrant tachycardia compared to patients with atrioventricular reentrant tachycardia. J Am Coll Cardiol 1995;25(Suppl. 1):255 [abstract].
[26] Hurwitz JL, German LD, Packer DL, Wharton JM, McCarthy EA, Wilkinson WE, Prystowsky EN, Pritchett EL. Occurrence of atrial fibrillation in patients with paroxysmal supraventricular tachycardia due to atrioventricular nodal reentry. Pacing Clin Electrophysiol 1990;13:705–10.
[27] Amasyali B, Kose S, Aytemir K, Kilic A, Heper G, Kursaklioglu H, Iyisoy A, Celik T, Kaya EB, Isik E. Atrioventricular nodal reentrant tachycardia with paroxysmal atrial fibrillation: clinical and electrophysiological features and predictors of atrial fibrillation recurrence following elimination of atrioventricular nodal reentrant tachycardia. J Interv Card Electrophysiol 2005;13:195–201.
[28] Tsuji H, Fujiki A, Tani M, Yoshida S, Sasayama S. Quantitative relationship between atrial refractoriness and the dispersion of refractoriness in atrial vulnerability. Pacing Clin Electrophysiol 1992;15:403–10.
[29] Otomo K, Suyama K, Okamura H, Noda T, Satomi K, Shimizu W, Kurita T, Aihara N, Kamakura S. Participation of a concealed atriohisian tract in the reentrant circuit of the slow-fast type of atrioventricular nodal reentrant tachycardia. Heart Rhythm 2007;4:703–10.
[30] Akhtar M, Damato AN, Batsford WP, Ruskin JN, Ogunkelu JB. A comparative analysis of antegrade and retrograde conduction patterns in man. Circulation 1975;52:766–78.
[31] Patterson E, Scherlag BJ. Anatomic and functional fast atrioventricular conduction pathway. J Cardiovasc Electrophysiol 2002;13:945–9.
[32] Spurrell RA, Krikler DM, Sowton E. Concealed bypasses of the atrioventricular mode in patients with paroxysmal supraventricular tachycardia revealed by intracardiac electrical stimulation and verapamil. Am J Cardiol 1974;33:590–5.